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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,633	08/22/2003	Elizabeth S. Light	03-776-D	9782

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/646,633	LIGHT ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213. .

Disposition of Claims

4)☒ Claim(s) *8-12 and 15-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 10/24/06. Claims 8, 9, 10, 11, 12 and 15 have been amended and claims 1-7, 13-14, and 17-22 have been canceled. Claims 8-12 and 15-16 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

2. Applicant's election of Group II in the reply filed on 10/24/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

3. The 112 2nd rejection previously set forth regarding high-risk HPV DNA and low-risk HPV DNA is MAINTAINED. Applicant argues that the use of the designations high-risk HPV DNA and low-risk HPV DNA are designations routinely used in the prior art to distinguish HPV that are associated with malignancy and those which are not associated with malignancy. However, while it is agreed that in the specification and in the prior art such terminology was commonly used, this does not mean that the use of such terminology clearly describes the metes and bounds of the claims. For example, Light et al. (1998) HPV type 70 is an "onocgenic HPV type" while the American Society for Colposcopy and Cervical Pathology include this type as a "low-risk HPV type" teaching that it is virtually never found in cancers (Medical FAQs on the

Natural History of HPV; p. 2 of 9). Although this terminology is widely used in the prior and post-filing date art, the metes and bounds of what makes an HPV type "high" or "low" risk are unclear.

4. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

The new limitation of which requires the "proportion of total HPV DNA in the reagent that comprises nucleic acid fragments of the first genomic HPV DNA probe set and the proportion of total HPV DNA in the reagent that comprises nucleic acid fragments of the third genomic HPV DNA probe set are decreased relative to the proportions of the total HPV DNA in the reagent..." in claim 9 appears to represent new matter. The specification provides a single example within this claim, but the specification does not provide any discussion or contemplation of this broad general subspecies. No specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. Since no basis has been identified, the claims are rejected as incorporating new matter.

The recitation that the reagent "is hybridized" at the conditions given in claim 10 appears to be new matter. While the specification teaches these conditions for a post-hybridization wash on page 14, the specification does not teach hybridizing the reagent at these conditions.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-12 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are drawn to methods for detecting human papilloma virus DNA in a cell sample, and requires the use of reagents which comprise a step of adding a reagent comprising a plurality of DNA probe sets to the cell sample, wherein the probe sets include genomic HPV DNA probe sets that comprise a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of each of HPV types 16, 18, 31, 33, 35, and 51, and wherein the fragments also hybridize to the genomic sequences of HPV types 39, 45, 52, 56, 58, 59, 68, and 70, but do not detectably hybridize to the genomic sequence of a low-risk HPV type.

In one respect the claims are quite narrow given the functional requirement that the assay utilize a probe set that does not detectably hybridize to the genomic sequence of a low-risk HPV type. However, this functional requirement is problematic from both a 112 2nd perspective (as previously discussed in this office action) and from a 112 1st paragraph perspective, as discussed in this Written Description rejection and in the following lack of enablement rejection.

Simply stated, the specification does not describe a reagent that does not detectably hybridize to the genomic sequence of a low-risk HPV type. This language clearly requires that the probe set which is used is one that does not hybridize to any "low-risk" HPV type. However, the specification exemplifies that even the most preferred probe cocktail disclosed hybridizes (in some cases) to "low-risk" HPV types.

The examples in the specification teach the preparation of a probes wherein plasmids containing the whole genome of HPV types 16, 18, 31, 33, 35, and 51 were labeled by nick translation with digoxigen dCTP (p. 8). The specification demonstrates that each of these individual probe reagents cross-hybridizes to some degree with other HPV types, some with other high risk types and some with other low risk types. For example, the HPV type 16 nick translated probe set detectably hybridized under the experimental conditions with types 6/11, 16, 31, 33, 35, 42, 43, 44, 51, and 58 (Example 1, p. 9). HPV types 6/11, 41, 42, 43, and 44 are all low risk types.

The "Present Probe Cocktail" hybridized detectably to one patient sample having HPV type 6/11 (low-risk HPV type) and also hybridized to samples which contained high-risk types. The specification states that "the present probe cocktail was shown not to give false positives with low risk of HPV types (p. 11)." However, Table 3 does show that a positive with low risk

type 6/11 was given for one patient. Likewise, the specification shows hybridization with low-risk HPV type 70 in three samples (p. 11)[1]. Example 3 shows results using low stringency and high stringency washes. In this example, the low risk HPV type 70 was detected using both high stringency and low stringency was conditions.

Thus, the specification does not actually describe a reagent that meets the limitations of the reagent used in the instant claims, since the instant claims require that the nucleic acid fragments of the genomic HPV DNA sets "do not detectably hybridize to the genomic sequence of a low-risk HPV type." The specification demonstrates that even the most preferred embodiments set forth in examples 2 and 3, and this reagent does detectably hybridize to the genomic sequence of a low-risk HPV type.

The instant claims are quite broad with respect to the structural features of the reagent which is set forth in part (a) of claim 8. However, the instant claims are much broader in nature than what is described in the specification with regard to what nucleic acid is required to be in the probe and how much of that nucleic acid. Instant claim 8 is sufficiently broad so as to encompass "genomic HPV DNA probe" sets for each of the six wherein the set has fragments having different sequences that detectably hybridize to a plurality of different nucleotide sequences "of essentially the full-length genomic sequence" of the particular HPV type. Thus, for each HPV type, it is required that there are fragments of different sequences, and that these must hybridize to essentially full length HPV. The claim is extremely broad, however, as to how much of the essentially full length HPV must be hybridized to- do the plurality of different nucleotide sequences have to amount to 50% of the essentially full length HPV? 75%? The only

[1] The American Society for Colposcopy and Cervical Pathology describes HPV type 70 as a low-risk HPV type (see

structural feature set forth to describe each probe set is that it comprise a plurality of nucleic fragments having different nucleotide sequences.

Claim 9 sets forth general requirements that HPV types 16 and 31 have lower representation in the probe reagent than the other listed types, but this disclosure is still quite broad in nature since it allows for any possible proportions within this generic requirement.

Claim 15 clearly sets forth the proportions of the probe in the set, but this claim remains broad in nature because of the broad nature of the description of the "fragments having different sequences" and the lack of adequate description as to how much actual HPV genomic sequence must be represented in each individual probe set.

It is clear that the specification describes that a method which uses combination reagent which was comprised of different proportions of the individual HPV types- namely it contained 8.3% HVP 16 and 31 nick-translated DNA and 20.8% of each of HPV 18, 33, and 51 nick-translated DNA. However, the specification does not provide any additional reagents where the proportions of HPV types vary within the reagent or reagents which meet the functional requirements of the claims.

Additional dependent claims included in the rejection recite additional method steps which do not further describe the probe set used in the claimed invention.

The claims do not set forth any particular sequences or structure for the probes, and in fact only identify the claimed nucleic acids in terms of their function. These claims encompass any set of oligonucleotide probes which would hybridize specifically to the recited types. As noted, the claims require that the sequence fragments hybridize to "essentially full length

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enclosed document "Medical FAQs on the Natural History of HPV," page 2 of 9.

genomic sequences," but this recitation does not limit the length of the probe fragments, or the composition of the probe fragments. An oligonucleotide of 30 bases could hybridize to a full length genomic HPV DNA molecule, or 50 bases or 100 bases. The fact that the probes must hybridize to an essentially "full length" molecule does not mean that the probes themselves must be full length. Further, the definition of "full length" in the specification is inclusive of "sequence variations and shortening of the probe length (specification page 5)."

The specification does not provide any description of the critical features of the single disclosed probe set which allow it to hybridize in the fashion described in the specification- namely that it hybridizes to the genomic sequences of HPV types 16, 18, 31, 33, 35, and 51, and additionally to types39, 45, 52, 56, 58, 59, 68, and 70. Therefore, there is no description of how the single disclosed probe reagent could be modified and still retain the feature that applicant purports in the arguments and claims to be critical to the invention.

From applicant's specification, Applicant does not appear to be in possession of a single probe combination which meets the functional limitations of the instant claims. Applicant is clearly in possession of a probe set that comprises probes that were produced by nick-translation of the full length genome of six separate plasmids, with one plasmid containing the whole genome of a HPV type and the six types being 16, 18, 31, 33, 35, and 51, wherein types 18, 33, 25, and 51 are present at 0.5 nanograms per milliliter of solution and types 16 and 31 are present at 0.2 nanograms per milliliter of solution (see p. 13, example 3).

Thus, even if the functional requirement of the claim regarding which the "does not hybridize language" were removed, applicant has express possession of only one species in a genus which comprises many, many different possibilities.

With regard to the written description, all of these claims encompass reagents comprising nucleic acid sequence different from those disclosed in the specific reagents which for which no written description is provided in the specification.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only a single reagent meeting the functional limitations of the claims is described, yet hundreds of thousands of possible reagents are encompassed by the claims. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of reagents modified from the single example given but possessing the functional characteristics required by the claims.

5. Claims 8-12 and 15-16 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The scope of the claims and the teachings in the specification are discussed in the written description rejection.

The prior art provides a wide variety of teaching regarding HPV cocktail probes. The prior art reference of Nuovo (1998) teaches an HPV consensus probe that hybridizes to HPV types 16, 18, 30, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 70, but not HPV type 6, 11, 42, 43, and 44. In this reference, HPV 70 is considered a "high risk" type. Nuovo et al. do not disclose any information about the content of the consensus probe, and applicant argues in the remarks filed 10/24/06 that the reference does not provide enabling disclosure of the reagent because the composition of the consensus probe is not provided, and thus, using the reference, a person of ordinary skill in the art would not be able to determine the particular HPV types or proportions of the particular HPV types without undue experimentation. The disclosure differs from the instant claims and disclosure because the instant specification teaches a reagent which comprises probes produced by nick-translation from six particular HPV types. The specification teaches that when these nick-translation products are combined in a very particular ratio, results identical to those provided by Nuovo (1998) are obtained. There is no disclosure in the specification of additional probe reagent. Following applicant's reasoning set forth in the declaration by Gerard J. Nuovo and in the arguments provided by applicant, it would require undue experimentation for one of ordinary skill in the art to modify the specific reagent taught in the specification to arrive at a reagent that meets the functional limitations of the claims. First, as noted, the single disclosed cocktail does not meet the limitations set forth in the claims. Second, even if it did, determining additional reagents which meet these limitations would

require extensive experimentation and screening of samples using reagents with differing compositions- where the content of the probe sequences in the reagent were varied, where the concentrations of relative HPV types were varied, indeed, where the HPV types themselves included within the reagent were varied.

Applicant states in their declaration "Using the teachings of my 1998 reference and knowledge in the art at the time my 1998 reference was published, a person of ordinary skill in the art...would not be able prepare a high-risk HPV consensus probe that does not detectably hybridize to the genomic sequence of low-risk HPV type."

The instant specification does not provide any further guidance as to how the single disclosed embodiment could be modified and arrive at a probe set that functions in the same way. The specification does not provide additional guidance. As noted by the declaration and applicant's arguments, it is highly unpredictable which formulations of the probe sets will cross-hybridize with the low-risk HPV types. Indeed, applicant's specification demonstrates this unpredictability since the preferred cocktail hybridizes in some instances with the low-risk types. Thus, in light of all of the evidence on the record, it is concluded that it would require undue experimentation to make and use the claimed invention.

Response to Remarks

The previously set forth rejections under 102 and 103 are overcome by applicant's arguments and declaration.

The written description rejection is modified to address the amended claims and maintained. Applicant states that the instant specification describes the HPV probes of the

invention as "essentially full length genomic HPV probes." However, the claims do not describe the probes this way. Limitations from the specification are not read into the claims. This is a feature not claimed. Applicant points out that the specification clearly contemplates methods of using reagents comprising various combinations of HPV genomic DNA probe sets, and points out that the claims have been amended to recite that the probe sets must hybridize to certain types of HPV. The claims still are not supported by an adequate written description for the reasons stated in the rejection.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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Juliet C. Switzer
Primary Examiner
Art Unit 1634

January 8, 2007